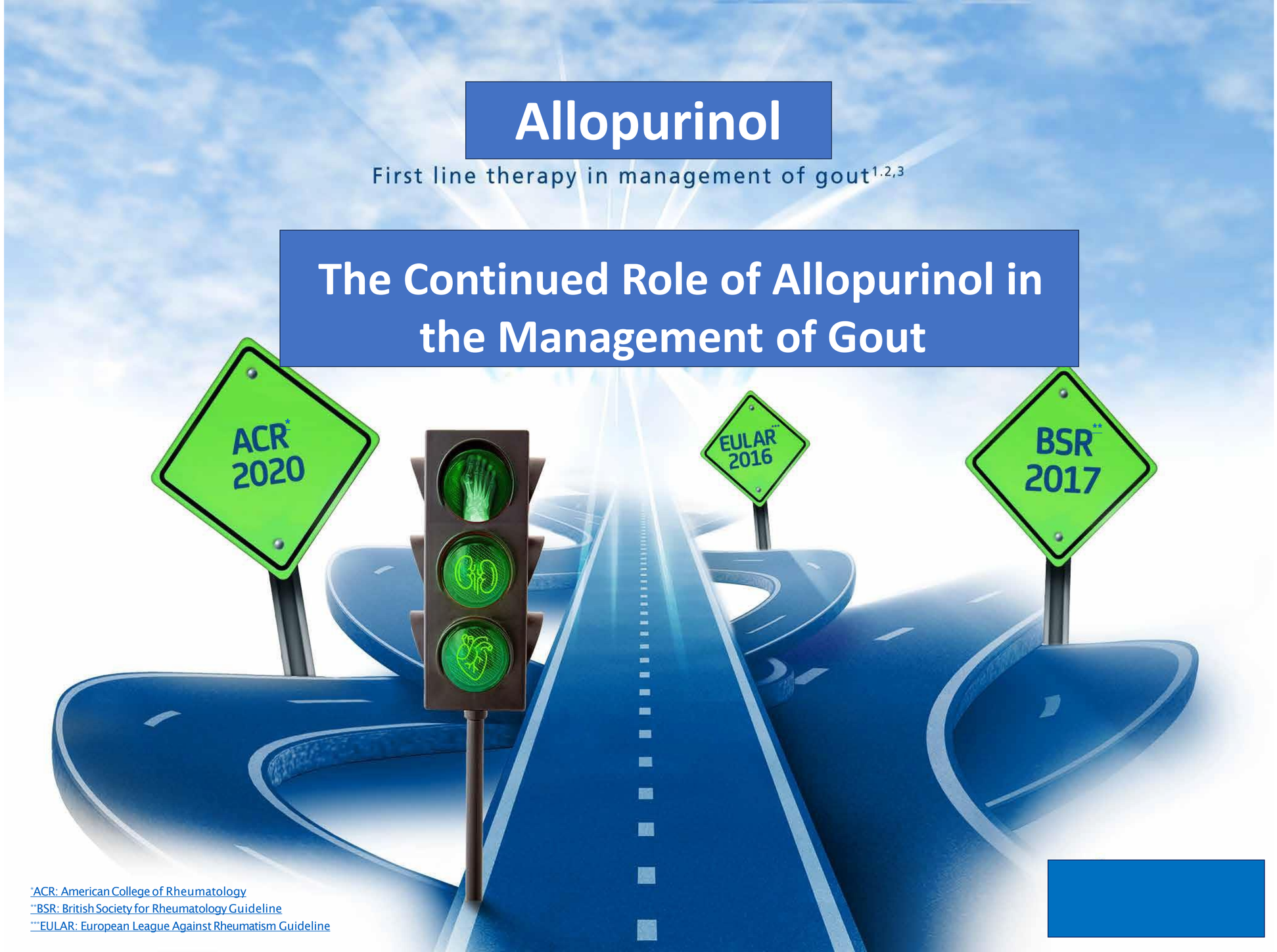
Allopurinol

First line therapy in management of gout[1,2,3]

The Continued Role of Allopurinol in the Management of Gout



*ACR: American College of Rheumatology
**BSR: British Society for Rheumatology Guideline
***EULAR: European League Against Rheumatism Guideline

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5 decades

FIRST LINE URATE LOWERING THERAPY FOR GOUT PATIENTS[1,2,3]

FDA APPROVED

First Urate lowering Agent

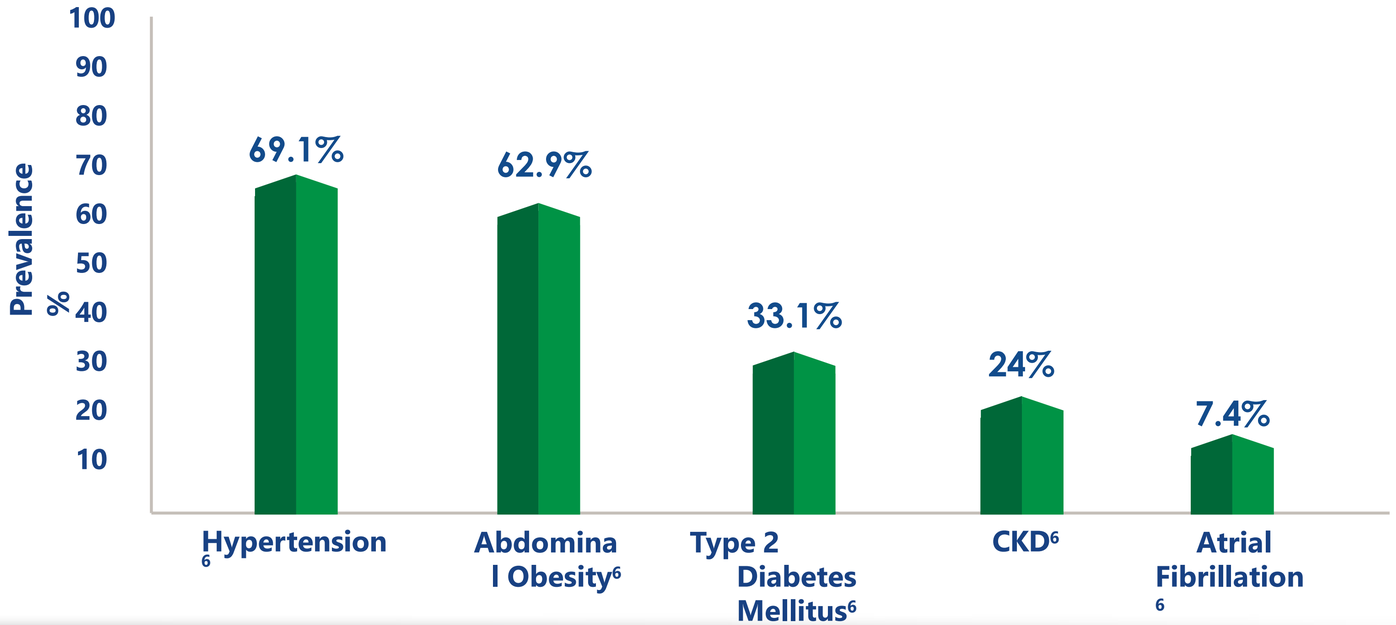
Allopurinol is a xanthine oxidase inhibitor that reduces uric acid

- Gouty Arthritis
- Idiopathic gout
- Uric acid lithiasis (Uric Acid Kidney Stones)
- Neoplastic diseases with high cell turn over

Every person with gout should be systematically screened for associated comorbidities and cardiovascular risk factors, including renal impairment, coronary heart disease, heart failure, stroke, peripheral arterial disease, obesity, hyperlipidaemia, hypertension, diabetes and smoking, which should be addressed as an integral part of the management of gout.[3]

(EULAR 2016)

The prevalence of comorbidities is high in gout patient



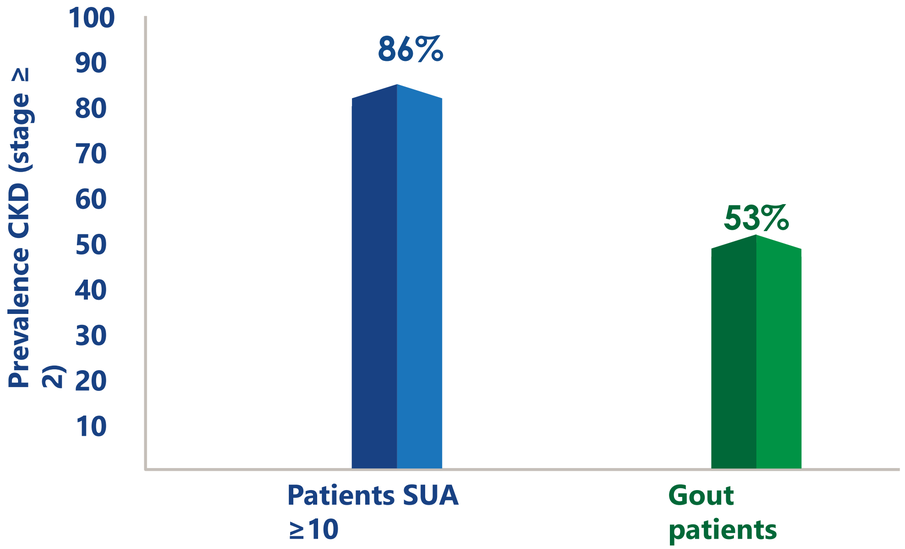
Gout is associated with premature death explained by high frequency of comorbidities specially with renal and cardiovascular diseases[6]

CKD: Chronic Kidney Disease

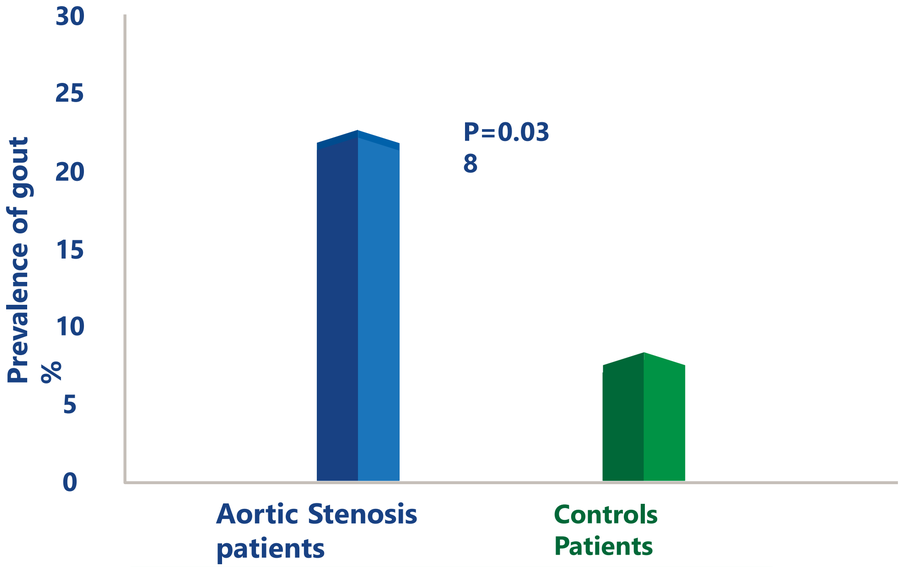
Every person with gout should be systematically screened for associated comorbidities and cardiovascular risk factors, including renal impairment, coronary heart disease, heart failure, stroke, peripheral arterial disease, obesity, hyperlipidaemia, hypertension, diabetes and smoking, which should be addressed as an integral part of the management of gout.[3]

(EULAR 2016)

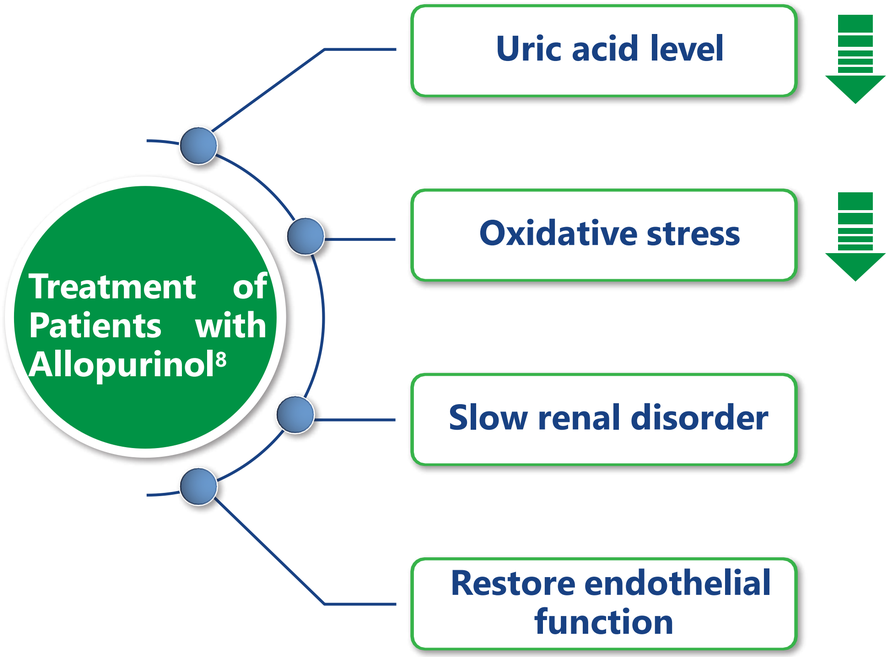
CKD appears to be a major risk factor for gout and, conversely, gout might cause renal dysfunction.[6]



The presence of gout was associated with approximately twice the risk of incident aortic stenosis compared to subjects without gout.[7]



Prevalence of gout history in aortic stenosis cases and non-aortic stenosis control.



- Epidemiological studies suggested that Allopurinol might decrease morbidity and mortality in patients with congestive heart failure and a history of gout.[3]

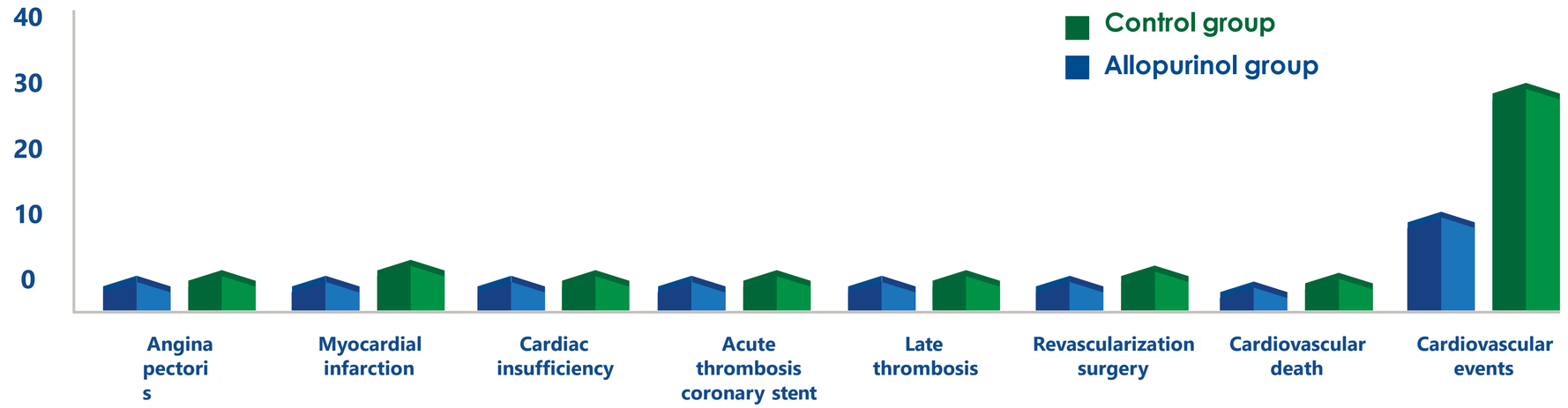
(EULAR 2016)

Pharmaco-epidemiological studies report that Allopurinol use is associated with an **20%** reduction approximately in myocardial infarction risk.[3]

(EULAR 2016)

Allopurinol has remarkable effect in the treatment of acute coronary syndrome and can improve the oxidative stress and inflammatory reaction indicators of patients[9]

Data collected during the 2 years follow-up period show that the incidence of cardio vascular events in the Allopurinol group is markedly lower than in the control group.




ACR
2020
EULAR
2016
BSR
2017

ACR* 2020 Management Guidelines[1]

Recommendations for choice of initial ULT*** for patients with gout [1]

- **Treatment with Allopurinol as the preferred first-line agent, over all other ULTs***, is strongly recommended for all patients, including those with moderate-to-severe #CKD (stage ≥3).**
- **For Allopurinol and Febuxostat, we strongly recommend starting at a low dose with subsequent dose titration to target, over starting at a higher dose (e.g., and lower in patients with CKD**)**

TREAT-TO-TARGET management strategy is strongly recommended:[1]

- ULT** dose titration,
- Subsequent dosing guided by serial SU measurements,
- To achieve a target SU, over a fixed-dose ULT** strategy.
- Achieving and maintaining an SU target of **<6 mg/dl** over the use of no target is strongly recommended for all patients receiving ULT**.

#CKD: Chronic Kidney Disease; **ULT: Urate Lowering Therapy;

British Society for Rheumatology Guideline[2]

First-line ULT **: Allopurinol

Start at low dose 50 - 100 mg daily.

Titrate Allopurinol dose in 50 - 100mg increments every 4 weeks dependent on SUA#

Target SUA# : < 300 µmol/L

Maximum dose 900 mg daily (dependent on renal function)

consider prophylaxis (colchicine 500 µd-bd or NSAID/coxib + PPI)

Do not stop Allopurinol during acute attacks

The British Society for rheumatology guideline for management of gout rheumatology oxford 2017

ULT** : Urate Lowering Therapy;SUA#: Serum Uric Acid

European League Against Rheumatism Guideline[3]

Initiate ULT**

History of allergy to Allopurinol

Start Allopurinol 100 mg/day
Adapt the dosage to the renal function.
Slow titration up to the maximum allowed dosage.

Achieve target

No

yes

Switch to Febuxostat or Switch to a uricosuric

Start Febuxostat or a uricosuric

Continue

Achieve target

No

Consider a combined therapy (XOI and a uricosuric)

Achieve target

No

yes

Continue

SUA# target not achieved

Start pegloticase

ULT**: Urate Lowering Therapy; SUA#: Serum Uric Acid

For patients with gout taking Febuxostat with a history of CVD * or a new CV event, we conditionally recommend switching to an alternative ULT agent if available and consistent with other recommendations in this guideline[1]**

Safety Announcement

[2-21-2019] The U.S. Food and Drug Administration (FDA#) has concluded there is an increased risk of death with (Febuxostat) compared to another gout medicine, Allopurinol. This conclusion is based on our in-depth review of results from a safety clinical trial that found an increased risk of heart-related death and death from all causes with Uloric(Febuxostat).[11]

ULT:** Urate Loweing Therapy
CVD***: Cardiovascular Disease
FDA#: Food and Drug Administration

Cardiovascular Safety of Febuxostat or Allopurinol in Patients with Gout for the CARES Investigators[10]

Table 2.. Major Safety Endpoints (Modified Intention-to-Treat Analysis).*

End Point	Febuxostat (N=3098)	Allopurinol (N=3092)	Hazard Ratio (95% CI)	
	no. of patients (%)			
Primary end point: composite of cardiovascular death, nonfatal myocardial infarction, non-fatal stroke, or urgent revascularization due to unstable angina	335 (10.8)	321(10.4)	1.03 (0.87-1.23) ‡	0.66 (0.002)
Secondary end points				
Cardiovascular death	134 (4.3)	100 (3.2)	1.34 (1.03-1.73)	0.03
Nonfatal myocardial infarction	111 (3.6)	118 (3.8)	0.93 (0.72-1.21)	0.61
Nonfatal stroke	71 (2.3)	70 (2.3)	1.01 (0.73-1.41	0.94
Urgent revascularization for unstable angina	49 (1.6)	56 (1.8)	0.86 (0.59-1.26)	0.44
cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke	296 (9.6)	271 (8.8)	1.09 (0.92-1.28)	0.33
Death from any cause	243 (7.8)	199 (6.4)	1.22 (1.01-1.47)	0.04

*The modified intention-to-treat analysis included all patients who underwent randomization with the exception of the 8 patients who never received febuxostat or Allopurinol.

† The P value in parentheses is for test of the null hypothesis that the hazard ratio is at least 1.3 versus the one-sided alternative (noninferiority). All other P values are values for the test of superiority of febuxostat to Allopurinol and were calculated with the use of a Cox regression analysis.

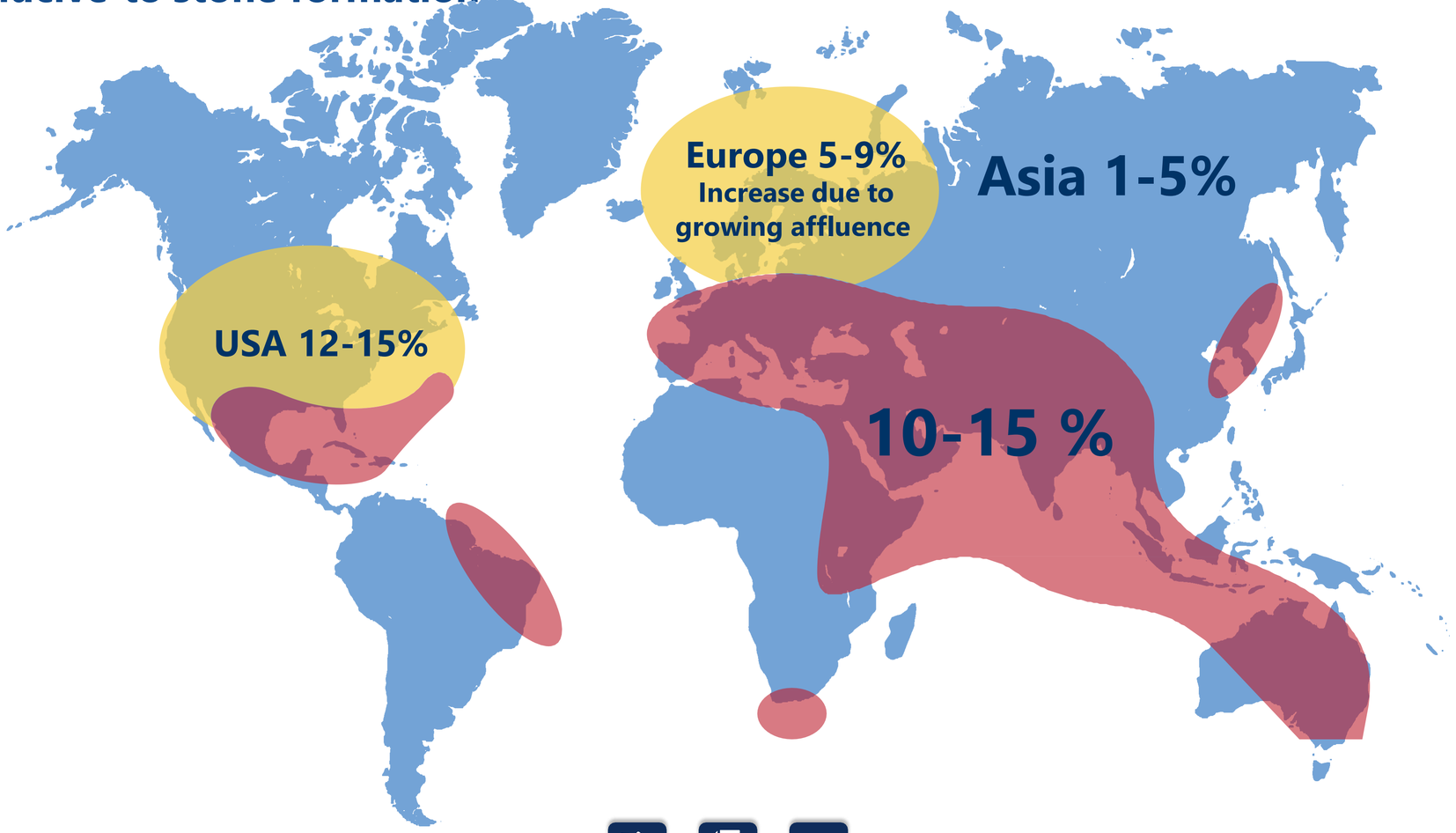
‡ The 97% confidence interval is provided here.

Higher all-cause mortality, resulting from an imbalance in cardiovascular deaths, was observed with Febuxostat than with Allopurinol.[10]

Febuxostat, however, was associated with a higher risk of CVD-related death and all-cause mortality (driven by CVD deaths) compared with Allopurinol[11]

Urolithiasis

Stone belt (red) extends all the way around the world and is characterized by urinary stone prevalence of 10 to 15%. In this zone the climatic and social conditions are conducive to stone formation.[12]



Risk factors associated with kidney stone formation[13]

No.	Risk Factors
1	Lifestyle habits and dietary/mtritiomal factors. such as excessive intake of animal proteins and salt and deficiencies of chelating agents like citrate, fiber, and alkali foods
2	Metabolic disorders such as hypercalciuria, hypocitraturia,hyperoxaluria, and history of gout (defective metabolism of uric acid)
3	Hypercalcemic disorders: primary hyperparathyroidism and other distrurbance of calcium metabolism
4	Urine composition: excessive excretion of promoters of urinary crystallization and reduced excretion of inhibitors (urine deficient in inhibitory substances)
5	Low urine volume: inadequate water intake (dehydration and supersaturated urine)

- About 5–10% of all stones are formed from uric acid.[14]
- A diagnosis of uric acid urolithiasis is supported by the presence of a radiolucent stone in the face of persistent urine acidity, in conjunction with the finding of uric acid crystals in fresh urine samples.[15]
- Patients with inflammatory bowel disease (Crohns disease, ulcerative colitis) tend to have hyperoxaluria and form oxalate stones. These patients also have a tendency to form urate stones.[16]
- Patients with hyperuricosuria can be treated with Allopurinol which will reduce urate formation. Urine alkalinization may also be helpful in this setting.[15]

Pharmacological Treatment of Urolithiasis

- Pharmacological treatment is necessary in patients at high risk for recurrent stone formation. The ideal drug should halt stone formation, have no side effects, and be easy to administer. Each of these aspects is important to achieve good compliance.[16]

AGENT	RATIONALE	DOSE-ADULTS	SPECIFICS AND SIDE EFFECTS	STONE TYPE
Allopurinol	Hyperuricosuria Hyperuricaemia	100-300 mg/d	▸ 100 mg in isolated hyperuricosuria ▸ Renal insufficiency demands dose correction	▸ Calcium oxalate ▸ Uric acid Ammonium urate 2,8 Dihydroxyadenine

(2013) Guidelines on Urolithiasis European Association of Urology C. pp:1-100

- In the setting of high urinary uric acid, normal urinary calcium and recurrent calcium oxalate stones, Allopurinol should be offered (Standard). However, Allopurinol should not be offered as first-line therapy for recurrent uric acid stones, as the underlying metabolic defect is typically a low urinary pH.[17]

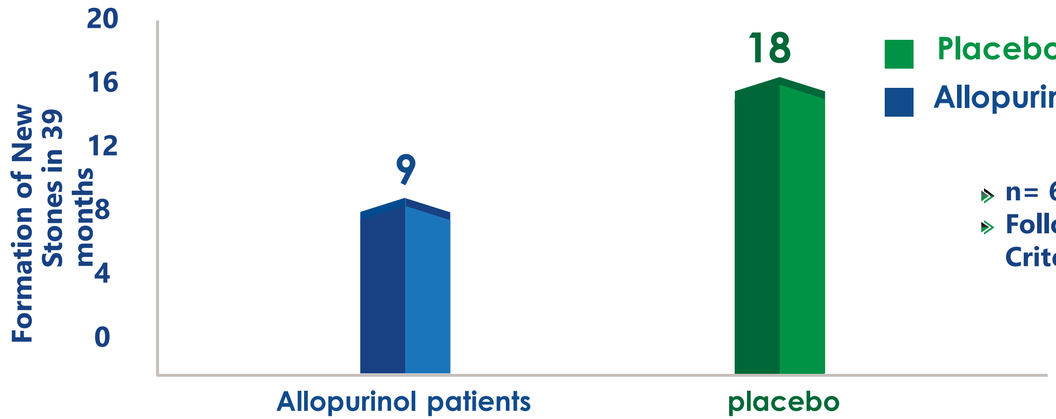
Risk factors associated with kidney stone formation[13]

- Stone types treated with Allopurinol are uric acid stones and calcium oxalate stones (only if uric acid is elevated in serum or urine).The main goal of Allopurinol treatment is to reverse hyperuricosuria and hyperuricemia.[18]
- Uric acid stone formers with a history of gout or documented hyperuricosuria refractory to dietary intervention may benefit from treatment with Allopurinol (100 to 300 mg daily).
- Recent investigations suggest a marginal role of hyperuricosuria in promoting calcium nephrolithiasis.[19]

Prevention of Urolithiasis evidence based medicine
Treatment of Calcium Nephrolithiasis in the Patients with Hyperuricosuria[20]

50%

Reduction
in new stone formation in favour of Allopurinol.



- n= 60 patients
- Follow-up: 6-39 month.
  Criteria:Patients with calcium oxalate urolithiasis.
  Patients who had two or more stones within 5 years and at least one stone within the last 2 years.

- It is concluded that Allopurinol is effective in prevention of calcium oxalate calculi and isolated
- hyperuricosuria. In addition, the Allopurinol group has a significantly longer time before recurrence

How to use

- **is introduced at low dosage 100mg/ day[4]**

100-200 mg Daily in mild conditions

300-600 mg Daily in moderately severe conditions

700-900 mg Daily in severe conditions

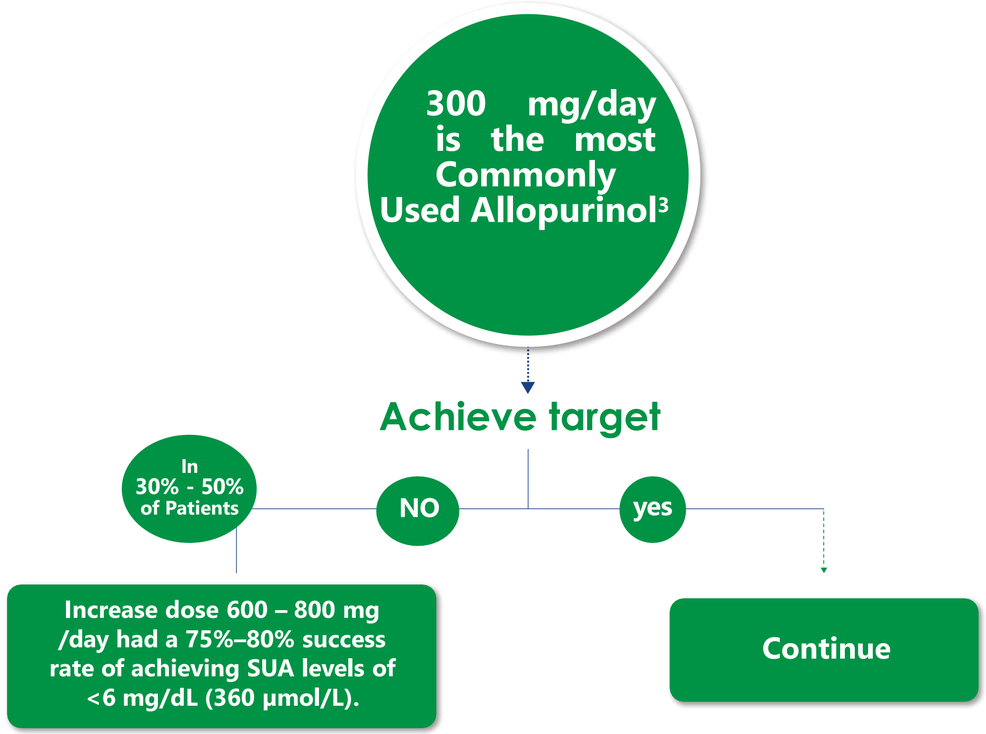
- **Low doses are used in renal /hepatic impairment and elderly.[4]**

SMPC

How to use

EULAR recommendations 2016 in dosage.

'Start low, go slow' approach is the recommended approach in the treatment of hyperuricemia,because it probably results in fewer episodes of acute gout during treatment initiation and therefore might improve ULT adherence[3]
(EULAR 2016).



- **In patients with renal impairment, the Allopurinol maximum dosage should be adjusted to creatinine clearance.**
- **The recommendation to initiate ULT earlier was mainly based on expert opinion but also took into account studies that suggest a cardiovascular and renal benefit from xanthine oxidase inhibitors (XOI).[3]**

- Allopurinol five decades first line compassionate therapy for gout patients.[1,2,3]
- Allopurinol showed cardiovascular and renal benefits for gouty patients.[3]

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